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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,062	01/21/2006	Anita Mehta	RLL-283US	1323

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EXAMINER	
SOLOLA, TAOFIQ A	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,062	MEHTA ET AL.	
	Examiner	Art Unit	
	Taofiq A. Solola	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-6, 9, 11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-6,9 and 11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action supersedes the last communication.

Claims 1-6, 9, 11-18 are pending in this application.

Claims 7-8, 10 are deleted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 9, 11-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amendment of the claims is new matter and must be withdrawn. The definitions of X and R5-R9 as H are removed. However, such must be done in the proper format and in accordance with the US patent practice. X is now defined as N. Such is not possible because N must have three bonds to it.

The claims lack adequate support in the specification. The term "aliphatic hydrocarbon group" (e.g. claim 1, line 19) is not defined in the specification so as to ascertain the structures of compounds that included and/or excluded by the term. There is no support for such in the specification. There is no conclusive evidence that such molecules are enabled by the process disclosed in the specification and if made there is no evidence such compounds would have the asserted utility. The only "hydrocarbon group" at position R7 made in all the examples is methyl. The term embraces far more complex molecules than are made in the examples. Steric hindrance and/or interference would more than likely be a problem and the specification

fails to disclose how such problem could be resolved. Applicant must show possession of the invention by describing it with all the claimed limitations. *Lookwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed Cir. 1997). In patent examination, it is essential for claims to be precise, clear, correct, and unambiguous. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir.1989). By replacing the term with alkyl the rejection would be overcome.

Claim 15 recites a temperature range of "from about 0-140° C. Such range is not supported in the specification. All the examples are made between 0 to room temperature. By deleting the claims the rejection would be overcome. See *Lookwood,* supra.

Claims 1-6, 9, 11-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for methyl at R7, for treating some of the listed diseases does not reasonably provide enablement for all possible hydrocarbon groups, for preventing or treating all respiratory, urinary and gastrointestinal (GI) diseases mediated by muscarinic receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

"'In the context of determining whether sufficient "utility as a drug, medicant, and the like in human therapy" has been alleged, It is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the [compounds and the utilities] as obviously correct." *In re Jolles*, 628 F.2d 1327, 1332 (Fed. Cir. 1980), citing *In re Novak*, 306 F.2d 924 (CCPA 1962); see 340 F.2d 974, 977-78 (CCPA 1965).

"A specification disclosure which contains a teaching of the manner and process of making and using the invention . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of

the statements contained therein which must be relied on for enabling support." *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), Id. at 1566, quoting *Marzocchi*, 439 F.2d 220, 223 (CCPA 1971); *Fiers v. Revel,* 984 F.2d 1164, 1171-72 (Fed. Cir. 1993), quoting *Marzocchi*, 439 F.2d at 223; see also *Armbruster*, 512 F.2d 676, 677 (CCPA 1975); *Knowlton*, 500 F.2d 566, 571 (CCPA 1974); *Bowen*, 492 F.2d 859 (CCPA 1974); *Hawkins*, 486 F.2d 569, 576 (CCPA 1973).

Where there is "no indication that one skilled in the art would accept without question [the instant compounds and method of use] and no evidence has been presented to demonstrate that the claimed products do have those effects *Novak*, 306 F.2d at 928, an applicant has failed to sufficiently demonstrate sufficient utility and therefore cannot establish enablement."' *In re Rasmusson,* 75 USPQ2d 1297 (CAFC 2005). The claimed invention is not enabled without undue experimentation for the following reasons:

For rejection under 35 U.S.C. 112, first paragraph, the following factors must be considered. *In re Wands*, 8 USPQ2d 1400, 1404 (CAFC, 1988): "The factors to be considered [in making an enablement rejection] have been summarized as a) the breadth of the claims, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and, the quantity of experimentation necessary, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex prate Formal*, 230 USPQ 546. The compounds embraced by the claims are so numerous and are in the hundreds of thousands or millions. The nature of the invention is using the compounds as pharmaceuticals. The specification fails to disclose any nexus between the instant compounds and treating/preventing all the claimed diseases. No biological assay is performed or published journals cited in support thereof. Such journals must have done the assay and applicant must incorporate the journals in accordance with the MPEP 608.01.

The term prophylaxis implies prevention. But, the specification fails to disclose how a "normal" human predisposed to all of the listed diseases would be identified and the diseases prevented. There is no absolute predictability or established correlation between the claims and the specification disclosures. The uncertainty presents one of ordinary skill in the art with obstacles and prevents her from accepting the invention on its face. Predictability in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. In the instant invention, there is no direction or guidance by applicant. There is no evidence in the specification that established correlation between the disclosure and the instantly claimed invention. *See Ex parte Mass*, 9 USPQ2d 1746, (1987).

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding any of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. By deleting prevention and limiting the diseases to those, which have support in the specification the rejection would be overcome.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-6, 9, 11-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For the reasons set forth above under 35 USC 112, first paragraph the claims are indefinite.

The term and "aliphatic hydrocarbon group" is not defined in the claims so as to ascertain the metes and bounds of the claims. Therefore, they are indefinite. See the Examiner's suggestions above.

Response to Argument

Applicant's arguments filed 12/14/07 have been fully considered but they are not persuasive. Applicant contends aliphatic hydrocarbon group is well known in the art. This is not persuasive because the requirement of 35 USC 112, is not what is known or obvious to one of ordinary skill in the art but a "full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same", *Lookwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed Cir. 1997). See also the status above. Applicant amends the utility claims form generic to subgeneric in some cases. This is not persuasive for reasons set forth above, and because some of the diseases as amended are not specific.

In responding to the rejection of claim 15, applicant refers the Examiner to page 10, lines 9-12 for support. Nothing in the cited passage is relevant to the claim. The passage on page 9, lines 10-13, referring to 0-140°C, is a mere speculation lacking conclusive evidence in support thereof.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 9, are rejected under 35 U.S.C. 103(a) as being unpatentable over Itho et al., EP 0 108986 A1, in view of Sugara et al., J. Med. Chem. (2002), Vol. 45(4), pp. 984-987, Takeuchi et al., EP 0 801 067 B1, and King, Med. Chem. Principle and Practice (1994), pp. 206-208.

Applicant claims compounds of formula I, composition thereof and method of use for treating respiratory, urinary and gastrointestinal (GI) diseases mediated by muscarinic receptors. In the compound, p and q are 0, therefore W and Y are absent; X is O or NH; Z is O, S or NR2 (R2 is H); Q is $(CH_2)_n$ (n is 1); R5-R9 are H and R10 is optionally substituted Aryl (phenyl). The compounds have bridged piperidine as cationic nitrogen-containing cyclic ring.

Determination of the scope and content of the prior art (MPEP 2141.01)

Itho et al., teach similar compounds, their composition and method of use for treating dysuria (urinary disease). In the compound, W and Y are absent; X is O or NH; Z and Q are CH_2; R5-R9 are H and R10 is phenyl. The compounds have piperidine as cationic nitrogen-containing cyclic ring. See the abstract, pages 2, 12-15.

Takeuchi et al., teach similar compounds, their composition and method of use as muscarinic receptors antagonist. The compounds have bridged piperidine as cationic nitrogen-containing cyclic ring. See the abstract, pages 2-4.

Sugara et al., teach essential features of muscarinic receptors antagonists as comprising an aromatic cluster, a spacer, a cationic nitrogen-containing cyclic ring and a hydrophobic site close to the ring. The compounds have piperidine as cationic nitrogen-containing cyclic ring. See page 984, Design and Synthesis and figure 2.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The difference between the instant invention and that of Itho et al., is that the cationic nitrogen-containing cyclic ring by applicant is a bridged piperidine instead of non-bridged piperidine by Itho et al. Also, Z is O, S, or NH by applicant instead of CH_2 by Itho et al.

The difference between the instant invention and that of Takeuchi et al., is that the bridged piperadine by applicant has 1,3-bridge instead of a 1,4-bridge piperadine by Takeuchi et al.

The difference between the instant invention and that of Sugara et al., is that the cationic nitrogen-containing cyclic ring by applicant is a bridged piperadine instead of piperidine by Sugara et al.

Finding of prima facie obviousness---rational and motivation (MPEP 2142.2413)

However, King teaches that replacement of CH_2 with O, -NH-, or -S- in a compound is expected to produce compounds having similar biological activity (bioisosterism). See page 208, bivalents. See also, *Ex parte Engelhardt,* 208 USPQ 343 (Bd. Pat. App. & Int., 1980); *In re Merck,* 231 USPQ 375 (Fed. Cir. 1986).

When R5-R9 is alkyl (as now amended) instead of H as in the compounds of Itho et al., such are as still obvious because H and alkyl are art recognized equivalents. *In re Lincoln*, 126 USPQ 477, 53 USPQ.40 (CCPA, 1942); *In re Druey*, 319 F.2d 237, 138 USPQ 39 (CCPA, 1963); *In re Lohr*, 317 F.2d 388, 137 USPQ 548 (CCPA, 1963); *In re Hoehsema*, 399 F.2d 269, 158 USPQ 598 (CCPA, 1968); *In re Wood*, 582 F.2d 638, 199 USPQ 137 (CCPA, 1978); *In re Hoke*, 560 F.2d 436, 195 USPQ 148 (CCPA, 1977); *Ex parte Fauque*, 121 USPQ 425 (POBA, 1954); *Ex parte Henkel*, 130 USPQ 474, (POBA, 1960).

None of the prior arts disclosed the specific bridged piperadine in the instant compounds. However, under the recent decision in *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727,-----, 82 USPQ2d 1385 (2007), obvious to try is now appropriate test of motivation.

When there is motivation

> to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under [35 USC] 103.

KSR Int'l Co. v. Teleflex Inc., 127 S.Ct 1727,-----, 82 USPQ2d 1385, 1397 (2007).

A person of ordinary skill would have known to replace CH_2 with O, -NH-, or -S- and piperadine with a bridged piperadine in the compounds of Itho et al., at the time the instant invention was made. The limited and available options are 1) a bridged piperadine with a bridge form between 1,3-carbon atoms, 2) ~~between 1,3-carbon atoms, or 3)~~ a bridge between 1,4-carbon atoms. These are identifiable and finite options. There is anticipated success because both bridged and non-bridged piperadine are successfully used in prior arts. Therefore, the instant invention is prima facie obvious from the teachings of Itho et al., Takeuchi et al., Sugara et al., and King.

Claims 11-12, 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sugara et al., J. Med. Chem. (2002), Vol. 45(4), pp. 984-987.

Applicant claims a process of making compounds of formula I, comprising the condensation of formula III with formula IV to form compounds of formula V, removing the protecting group from formula V to form VI and alkylating formula VI to form compound of formula I. In preferred embodiments, the protecting group is benzyloxy and the solvent is methanol.

Determination of the scope and content of the prior art (MPEP 2141.01)

Sugara et al., teach similar process of making compounds of formula I. The protecting group is benzyloxy and the solvent is methanol. See scheme 3, steps (c) to (e) and column 2, page 985, last paragraph.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The difference between the instant invention and that of Sugara et al., is that the starting reagents have different substituents and therefore, are analogous compounds.

Finding of prima facie obviousness---rational and motivation (MPEP 2142.2413)

However, the use of an analogous starting material in a well-known process is prima facie obvious. *In re Durden,* 226 USPQ 359, (1985). There is no evidence in the specification or the prior art that the substituents have any effect on the reaction process. Therefore, the instant invention is prima facie obvious from the teaching of Sugara et al. One of ordinary skill in the art would have known to change the substituents at the time the invention was made. The motivation is to avoid the prior art.

Response to Argument

Applicant's arguments filed 12/14/07 have been fully considered but they are not persuasive. Applicant contends argues against the prior arts individually based on the amendment of the claims. This is not persuasive for reasons set forth above.

Takeuchi et al., is cited to show the applicability of bridged piperadine in the instant invention, while Sagara et al, is cited to show the three main features of the inventive compounds. From the prior arts of Itho et al, Takeuchi et al., and Sagara et al., it is clear that the choice of any bridged or non-bridged piperadine is an obvious modification available to the preference of an artisan. Applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642

F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant also argues that none of the prior arts teach or suggest the claimed limitations. The argument is foreclosed by the recent decision in *KSR,* supra.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taofiq A. Solola, PhD. JD., whose telephone number is (571) 272-0709.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

TAOFIQ SOLOLA
PRIMARY EXAMINER

Group 1625

January 18, 2008